iGEM Cardiff_Wales

Transcripts of Interviews used as a template for Integrated Practices Essay section.

MHRA interview w Jo Groszewski

1) What role(s) do you play in getting a new diagnostic from concept to the market? Please elaborate. How long does this take? What costs are involved?

In vitro diagnostic medical devices must bear a CE mark before they can be placed on the market or put into service anywhere in the EU. The CE mark represents the manufacturer's declaration that the product meets all of the relevant requirements of the IVD Directive (98/79/EC). MHRA is the UK competent authority for this Directive and manages the regulatory system in the UK. We do not have a direct role in bringing products to market – instead we designate and monitor third parties (Notified Bodies) to assess higher risk products before they can bear the CE mark. Lower risk products can be self declared by the manufacturer without the involvement of a Notified Body. Registration with MHRA costs £79 and is usually completed within a matter of days. Notified Body fees will be higher and if required this process will take longer.

The IVD Directive is under review and we expect a new set of regulations to be published towards the end of this year or the beginning of next year. This would result in an upclassifcation of many IVDs including tests for STIs

2) In our design, we have focused on reducing the chance of false positives by designing a double Cas9 system to increase the fidelity of the reaction. How important is it to reduce false positives? Does MHRA or another body set a strict limit that has to be met?

IVD manufacturers are expected to manage risks as far as reasonably practical and maintain a positive risk/benefit ratio. Whilst there are some IVDs with minimum specifications (such as HIV testing in the common technical specifications and blood glucose testing in ISO 15197), the manufacturer is expected to declare their claimed performance, have sufficient evidence to support that performance and the IVD is expected to meet that performance throughout the lifetime of the device

3) What considerations are of utmost importance when processing a new medical device, such as a new diagnostic?

To place a Medical Device in the market the manufacturer will need to demonstrate that the medical device meets the requirements in the Medical Devices Directives by carrying out a conformity assessment. The CE mark can be placed in the product to show that the medical device has met the requirements when the product has passed the conformity assessment,

Further information can be found in the MHRA website.

https://www.gov.uk/guidance/medical-devices-conformity-assessment-and-the-ce-mark

https://www.gov.uk/government/publications/in-vitro-diagnostic-medical-devices-guidance-on-legislation

4) To what extent did MHRA play a role in the legalisation of HIV home testing kits? What did the process of helping to get HIV home testing kits to the market involve (e.g. risk assessments, technical requirements, legislation etc.)? Which people/external bodies were consulted?

Although MHRA where not the competent authority for this act, we worked closely with colleagues in the Department of Health and Public Health England as they put together the repeal. The strict regulatory requirements in the Common Technical Specifications for HIV testing was a key part of the strategy for the repeal of the Act

5) We spoke to a retired social worker who stated the importance of giving pre-test counselling to her 'patients' before they were tested for HIV, and a worry about people 'burying results'.

What do you think about the prospects of including pre-test counselling alongside HIV home testing kits, or consumers receiving a phone call after purchasing the kit to see how they are processing their results?

Also, what do you think about the positive impacts of such a test? What was involved in balancing the two in the legislation of home testing kits?

PHE produced a Q&A that addresses all of these questions - https://www.gov.uk/government/news/common-questions-on-hiv-testing-addressed-in-new-phe-publication

6) How does the regulatory process differ for the development of point of care tests used in a professional setting and for that of home testing kits? Also for different STIs, such as herpes or chlamydia?

To place a Medical Device in the market the manufacturer will need to demonstrate that the medical device meets the requirements in the Medical Devices Directives by carrying out a conformity assessment. The essential requirements aim to ensure that the products do not compromise the health and safety of patients and users, and are designed and manufactured to achieve the performance specified by the manufacturer for the stated medical purpose. Not all the essential requirements will apply to all devices and it is up to the manufacturer of the device to assess which are appropriate for his particular product.There are specific requirements for the regulation of home tests in the IVD Directive.

Please find further information regarding IVD regulations in MHRA guidance.

https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/404335/In_vitro_diagnostic_medical_devices_-_guidance_on_legislation.pdf

7) Do you think that the use of a CRISPR/cas9 system (such as dcas9) in a cell free kit has a future in the market for point of contact tests? Why?

MHRA supports safe innovation.

If yes, what would be involved, including regulations posed by the MHRA, to get such a product to the market 1) as home testing kit and 2) for use in a healthcare setting? And within what time scale?

8) How important is it for such a device to be 'cell-free' if it has GM-derived components in the regulatory process?

No specific response from MHRA, but you might want to have a look at a recent Dutch report on synthetic biology - http://www.rivm.nl/en/Documents_and_publications/Scientific/Reports/2016/augustus/Developments_in_novel_medical_products_with_modern_biotechnology_and_specifically_synthetic_biology_A_quick_scan

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To response to the proposed '**Survey on Home STI Diagnostic Kits'**

Dr Jillian Craigie
Lecturer in Medical Ethics
Centre of Medical Law & Ethics
Dickson Poon School of Law
King's College London

Most importantly, however, I would stress the importance of not just asking people what they think about these ethical issues, but seeking out relevant academic literature on this topic. It is there that you will find considered answers, and I strongly suggest that this is where you would want to place your emphasis in analysing your survey responses.

My main observations about the survey are:

(1) The emphasis in the answers is on the consequences of home testing for STIs rather than non-consequentist considerations such as rights or autonomy. So, for example, one might argue that people have a right to access this kind of technology and the information that it can provide ("freedom of knowledge") even if the consequences are unclear, neutral or negative overall. I'm not saying that this is right, but it is a point that would be worth bringing out. How should the two types of consideration be balanced?

(2) In terms of the responses that refer to consequences much of those are speculations about human behaviour and though I think these are important hypotheses to consider, most are no more than that. Surely there is empirical evidence out there, from other countries or even since 2014 in the UK, about how people respond when home testing is available.

Finally, you may want to look into what's happening in public policy in the UK. I understand that funding for sexual health services is being cut all over the country so it may be important to see all of this in the current political context.

Good luck!
Jill

Rachel Coombe- Cardiff University Biological Safety Officer interviewed with reference to the differences between cell-free and live/attentuated testing kits

General Questions:

1. Can you provide details about your role as Assistant Director (Scientific) for Safety and Staff Wellbeing?
   The Safety and Staff Wellbeing Division of Cardiff University provides competent advice to Cardiff University as required by a number of pieces of health, safety and environment legislation in the United Kingdom. I, as the Assistant Director (Scientific), have a number of duties and responsibilities. This includes providing professional advice and guidance on scientific safety and compliance processes and procedures to internal and external customers that will have institution-wide impact. With regard to the UK legislation on genetically modified organisms, I provide advice to the University as the competent person recommended in the guidance to the Regulations. The Scientific Support Officer of the Safety and Staff Wellbeing Division assists me in providing competent advice to the University. As the Biological Safety Adviser to the University I am the Secretary, and organise meetings of the University Genetic Modification and Biological Agents Safety Committee. I have the Administrative Assistant to help me in this task and other tasks related to administration of the Committee and work relating to genetically modified organisms.

2. Can you please provide an overview of the regulations that the University has to meet when researchers apply to work on GM projects?

   I can do no better than refer to the website of the Health and Safety Executive, please see http://www.hse.gov.uk/biosafety/gmo/law.htm .The Health and Safety Executive oversee health and safety legislation and its enforcement within the UK. The University essentially sets about complying with the GM (Contained Use Regulations) by

   i) Having a Genetic Modification and Biological Agents Safety Committee to review risk assessments of all work involving genetically modified organisms and work with hazard group 3 biological agents. No work of this description can start within Cardiff University until this Committee is satisfied with the risk assessment for the work.

   ii) All institutions or centres that carry out work with genetically modified organisms must be notified to the HSE. Cardiff University has been registered as a GM Centre with the HSE before re-registration, as required by an update to the Regulations, since 1 April 2002. The GM Centre Number is GM130.

   iii) GMO contained use activities of Class 2 or above must be notified individually to the HSE. This also attracts a notification fee. The Biological Safety Adviser assists with the notification process. Cardiff University has projects which are Class 1, Class 2 and Class 3 activities.

   iv) Prior to any work being allowed to start the facilities where the work is to be carried out are inspected by the Biological Safety Adviser or the Scientific Support Officer.

v) The persons responsible for each project are required to update the risk assessment for a project on a regular basis, if they suspect that the risk assessment is no longer valid or there has been a significant change in the contained use to which the risk assessment relates.

vi) The Health and Safety Executive visits Cardiff University on a regular basis to inspect the premises and procedures. Premises for Class 3 facilities are visited once every 3 years, other premises are visited at regular intervals.

vii) All new personnel involved in working with genetically modified organisms must attend the Cardiff University Safety Induction Course for GMO Workers. New personnel are expected to also receive School and local laboratory safety induction training. Records of all safety training must be kept.

viii) Currently Cardiff University does not have any "deliberate release work" involving genetically modified organisms. All the work at Cardiff University currently falls under the remit of the Genetically Modified Organisms (Contained Use) Regulations 2014.

3. Do you have any experience where current GM regulations have prevented a proposed project from being conducted at the University?

   I have worked for Cardiff University for 25 years and I have never been aware of GM Regulations preventing a proposed project from being conducted. There may have been delays to projects whilst compliance issues, eg refurbishment of an area or a laboratory, are resolved.

4. Have you observed about change in regulations in recent times?

   The essential requirements of this set of Regulations of contained use have not changed in recent times. There have been changes previously to take note of where large volumes of cultured genetically modified microorganisms were being used and there are slight differences to the approach for control measures for genetically modified animals and plants which are now called larger GMOs. Although there has also been some change in that there is a slight relaxation in the requirements for the disposal of very low risk genetically modified microorganisms, this is dependent on risk assessment and therefore most Institutions are ignoring the change. The change that happens on a reasonably regular basis is, however, is the cost of notification. This increases steadily to meet administrative costs of the HSE. The feeling of biological safety advisers is generally that some scientists responsible for GM projects are tempted not to notify their work or are tempted to join projects together to form a connected programme of work. Connected programmes of work are allowed, however they can be difficult to deal with as an administrative issue and for the Committee to be satisfied that projects are truly related. Forming connected programmes does obviously save the scientist/person responsible money from their research income.

5. What are your views about current public education and perception surrounding the topic of genetic modification?

I think this will improve gradually over time now that it is being included in the curriculum of courses in UK secondary schools. Public science education is also slowly improving, I think due to the engagement activities of the major universities and colleges in the UK.
Professor Nick Pidgeon of Cardiff University School of Psychology has carried out a great deal of research on understanding risk. A number of years ago he did a substantial amount of work on the public understanding of genetic modification concentrating on perception of the risk of genetically modified food and crops.

Project Specific Questions:

1. Our research project aims to design a diagnostic tool that will include genetically modified components. Do you have any experience with anything of this type and are you aware of any GM regulations that apply to diagnostic tools?

   Earlier in my safety career I was employed as Biological Safety Adviser for the University of Wales College of Medicine and contracted to provide advice to the precursor of Cardiff and Vale University Health Board. A test developed by UWCM went on to be used in the Biochemistry laboratories of the Hospital. This was all contained use and both institutions were registered with the HSE as GM Centres. Both sets of laboratories were up to the standard required to carry out GM work of that nature. Had this test gone on to be marketed as a diagnostic tool, it would have required the hospital department to seek advice from the HSE with regard to the Genetically Modified Organisms (Deliberate Release) Regulations 2002. Had they judged that this was a deliberate release, then the risk assessment would need to have been reviewed by a national committee - the Advisory Committee on Releases to the Environment (ACRE). The department would also have had to seek advice from the Medicines and Healthcare Products Regulatory Agency as a diagnostic testing kit would count as a medical device under the Medical Devices Directive. There is a specific In Vitro Diagnostic Medical Device Directive. The requirements of the Directive must be met before the device can be placed in the market. This is, however, an EEC Directive and so possibly further discussion would be straying to the realms of politics. Please see https://www.gov.uk/guidance/medical-devices-how-to-comply-with-the-legal-requirements.

2. Considering current regulations do you think it would be feasible to license a testing diagnostic test kit of this type?

   I think it would be possible but it would involve seeking advice from someone with more experience of the relevant Medical Devices Directive. However, I do think that the Safety and Staff Wellbeing Division could act as a means of approaching the HSE for advice with regard to whether this would be counted as deliberate release or an extended contained use.

3. We are planning on developing the tool either as a live-cell or a cell-free system (that contains GM components in a cell-free kit) so do you think either of these would be more straightforward to license?

   My knowledge of the licensing of medical devices is not wide enough to be able to fully answer this. However, just considering GM Regulations I think it would be simpler to license a cell free kit.

4. Would there be different regulations if a diagnostic kit was intended for use in a testing lab, by clinicians or for home use?

   Again simply from the GM regulatory point of view, within the testing lab, would definitely be Contained Use Regulations, for use by a clinician in a clinic or GP surgery would be considered as contained use - I have been the Biological Safety Adviser at an early stage clinical trial of a GM vaccine where a live GM vaccine was given to a patient in a hospital infectious diseases unit negatively pressurised cubicle. This was considered to be contained use as the vaccine was considered to be contained within the phial, then the syringe, then the person's body. After initial testing the vaccine was then used in an outpatient environment and the patient was allowed to go home wearing an occlusive dressing over the vaccine site and this was still considered to be contained use. I think for home use it would very much depend on how the regulatory bodies reviewed the work and the risk assessments. There are large numbers of vaccine trials now ongoing across the world that are considered safe and a number of such trials in the UK are considered to be contained use. All work considered to be gene therapy, which this was, must also be reviewed by GTAC (the Gene Therapy Advisory Committee) which is a national research ethics committee.

5. Could you predict the type of regulations that would be required in order for a product that contained GM components to make it to market?

   I think this would very much depend on results of initial testing within the laboratory and how the regulatory agencies, ie HSE for contained use and HSE and DEFRA for deliberate release, with involvement from the MHRA, would consider it.

Interview with Emily Engel, HIV specialist social worker (retired)

> On burying results and monitoring reactions/suicide rates/patient care

What is your experience with HIV patients? (how long you worked with them for, what your job involved etc.)

I worked as a specialist social worker with families with HIV for 10 years (the 1990's). I was based in a hospital for the first 5 years, so part of the job was also working with hospital staff and other groups such as nursery staff, home helps etc to get the policies right. One of the big risks was scaring the 'patients' off, as there was so much stigma and mis-information around at the time: it was important to adapt the systems to ensure women trusted the hospital, to make sure they came back to get the treatment they needed, and especially to allow their children to be tested and treated. There were frequent stories of people being publically 'outed', attacked and stigmatised.

What are your thoughts on home testing kits for HIV?

I am hesitant about home HIV testing kits because of the risk that it supports secrecy and denial. If people think they are at risk of HIV, they need to take on board a whole load of implications for their every day behaviour, which very few people will be able to manage without support. If they dont seek that support, they may be tempted to simply bury the result and continue to put themselves and their sexual partners at risk. Drug treatment nowadays can reduce infectiousness and greatly reduce the risk of HIV-related illness, but it depends on acknowledging a need to change behaviour, maybe even lifestyle, and taking responsibility. This can be especially difficult for young gay men, or women, or anyone who has not lived among those who are open and familiar with HIV.

What did your pre-test counselling involve?

Pre-test counselling is different to conventional counselling insofar as it involves being more directive, getting people to think forwards to the different outcomes so they can make fully informed decisions. So it involves considering their experiences and relationships and who else might need to know, how a negative test might change their life as well as a positive result. It often means the person will go away and think, and maybe talk to friends & partners, to make the decision with their eyes wide open. This is the element that can so easily be avoided with a mail-order home test...

Did you experience patients who you thought were reluctant to notify local authorities? Please elaborate.

Local Authorities did not need to be notified: HIV was never classified as a notifiable disease precisely because of the knowledge this would stop people coming forwards for diagnosis / treatment.
But many many people went through phases of resisting the changes they needed to make, including telling their partners, and needed a lot of support to come to terms with this: after all, it is a life-changing diagnosis, even if it isn't a terminal diagnosis anymore. Changing your life usually takes a while to sink in, even when it's an instantaneous event.
Doctors have a duty to public health, but they were reluctant to use it to breach someone's confidentiality as the risk of losing the patient, causing a much bigger risk... sometimes I

did hear them become pretty firm, telling someone if they didn't bring their partner in to the next appointment, they'd have to invite them personally!

As a social worker, this was a core part of the work, helping people to see the wider implications of various courses of action and make the best decisions in the circumstances.

How important do you think pre-test counselling is, and do you think pharmacists could and/or should provide this for people who buy these tests?

I doubt that most pharmacists would want to do more than just pose the most obvious questions: they'd need private consultation space and a great deal of training and time to take the task on, and it's not really like any other part of their job, so I think the best solution is for a specialist service to be widely available, in a completely neutral setting (i.e. not an STD clinic or the GP surgery!)

Using home testing kits:
What sort of outcomes do you envisage from the positive result of a home testing kit?

Ideally, a home testing kit should come with information about the nearest support service - support for those with a negative result to avoid repeated exposure / fears, as well as for those who get a positive result. And some follow-up: a call a few days later to check if the person's done the test and is OK / following up appropriately.

Do you think there should be regulations or profiling?

mmmm..... I guess I'd prefer that there was no demand for home testing. Regulation is not going to be effective in the privacy of home testing. And I'm not sure what you mean by profiling?

More of your opinions-
Effects in relation to situation (e.g. pregnancy) and suicide rates.

HIV testing is offered routinely in ante-natal clinics, and I suspect that here's very little training in how to manage it properly. It's a terrible time to get such a diagnosis – specially since it probably has very complex implications, such as did your partner know, are there older children who might be infected, or will this mean your drug use is now public, with all the judgements that carries as far as mothering is concerned...
There is ample evidence that suicide rates among gay men after diagnosis shoots up (7 to 36 times the average rate - Coté TR, Biggar RJ, Dannenberg AL. Risk of suicide among persons with AIDS: A national assessment. *JAMA* 1992), and some indication that it's even greater for women (Cooperman & Simoni, J Behav Med. 2005 Apr;28(2):149-56 – not a great ref - http://positivelyuk.org/wp-content/uploads/2015/09/Women-Know-Best-Report_Final-Aug-15.pdf is an excellent report & overview.)

Do you have any further comments you want to make on the topic in relation to your experience, policies, potential regulations, ways to get around problems etc?

I could go on a long time... but my knowledge is out of date, it's 15 years since I left the HIV world and much has changed. Also, I never worked with gay men much, and there are quite different & specific issues for women, whether they've been aware of being at risk (e.g. because they inject drugs) or not...

Interview with Dr Patrick Hardinge- Research Associate at Cardiff University who works on a diagnostic using BART-LAMP amplification (Lumora):

In relation to our project, and his work:

Sensitivity and false positives

"[The project] sounds really good. I suggest that a double cas-9 may be better as it would increase the specificity of the reaction to reduce false positives. In my work with diagnostics using firefly luciferase and the BART-LAMP amplification system, specificity is a very important consideration. One strength of our system comes from its use of multiple primers, which increases specificity and boosts speed."

"Sensitivity is vital. We are aiming to identify a low number of DNA templates copies, in the range of 1-10 copies.. For that level of sensitivity we need well-designed primers, and optimal conditions. There is a lot of trouble-shooting involved to get it just right."

Designing a machine for a potential product

"Of course, a machine must be designed to detect light output. You can use a photon imager in the lab [to quantify the emission] but this costs a >£100K. For this, it is best to use something that just detects light to keep costs down. A CCD camera or a photodiode, which can cost a penny, is suitable."

"It is then necessary, to distinguish between the background and the luciferase clearly. So I test it using BART, which has the distinct characteristic of switching off rapidly. As the reaction goes on, (for an hour?), the pyrophosphate builds up, and inhibits the luciferase- the light emission eventually drops."

Emily Rosselli at Terence Higgins Trust referred me to this during a phone conversation

http://www.tht.org.uk/our-charity/Media-centre/Blog/2016/July/Groundbreaking-projects-are-changing-lives,-thanks-to-lasting-legacy-of-the-Lighthouse

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Nadia Ramjhun at National Aids Trust referred me to this after a phone conversation

http://www.bhiva.org/documents/Conferences/2016Manchester/Presentations/160421/MichaelBrady.pdf Link to presentation given at BHIVA conference.